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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/569,076	08/23/2006	Wolfgang E. Berdel	20490.003	7498

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EXAMINER	
ALLEN, MARIANNE P	

ART UNIT	PAPER NUMBER
1647	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/569,076	BERDEL ET AL.	
	Examiner	Art Unit	
	Marianne P. Allen	1647	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *19-40* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *19-40* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *5/18/06*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Claims 1-18 have been cancelled. Claims 19-40 have been newly introduced in the preliminary amendment filed 2/21/06.

Specification

The substitute specification filed 2/21/06 has been entered.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 19-40 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for the fusion polypeptide of SEQ ID NO: 3, nucleic acids encoding SEQ ID NO: 3, vectors and host cells containing this sequence, and methods of treatment by administering the fusion polypeptide of SEQ ID NO: 3, as set forth below, does not reasonably provide enablement for all fusion polypeptides, nucleic acids, vectors, cells, and methods of treatment embraced by the claims. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

Claims 19-28 are directed to fusion polypeptides. Claims 34 and 38 are directed to a pharmaceutical composition comprising a fusion polypeptide.

Claims 29-30 are directed to nucleic acids encoding fusion polypeptides.

Claim 31 is directed to a vector and claims 32-33 are directed to cells.

Claims 35-37 are directed to pharmaceutical compositions comprising a nucleic acids, vectors, and cells, respectively.

Claims 39-40 are directed to methods of treating a patient with neoplastic disease by administering a fusion polypeptide.

The specification discloses production of specific fusion proteins, including cyclic fusion proteins:

tTF-GRGDSP (SEQ ID NO: 3; Fig. 14; designated tTF-RGD)

tTF-GNGRAHA (SEQ ID NO: 4; Fig. 15; designated tTF-NGR)

tTF-GALNGRSHAG (SEQ ID NO: 5; Fig. 16)

tTF-GCNGRCG (SEQ ID NO: 6; Fig. 17; designated tTF-cycloNGR1)

tTF-GCNGRCVSGCAGRC (SEQ ID NO: 7; Fig. 18; designated tTF-cycloNGR2)

tTF-GCVLNGRMEC (SEQ ID NO: 8; Fig. 19; designated tTF-cycloNGR3)

SEQ ID NOS: 3-8 are recited in claim 28. These sequences are encoded by SEQ ID NOS: 10-15, respectively. SEQ ID NOS: 10-15 are recited in claim 29. SEQ ID NOS: 33-38 are recited in claims 26-27 and form the peptide part of SEQ ID NOS: 3-8.

Tumor selectivity is disclosed as being due to the specificity of the RGD sequence for $\alpha_v\beta_3$-integrin and of the NGR sequence for CD 13 (aminopeptidase N). These receptors are disclosed as being expressed selectively and specifically at high density on tumor endothelial cells.

Only the fusion polypeptide of SEQ ID NOS: 3 was evaluated for selectively binding to $\alpha_v\beta_3$-integrin on endothelial cells (see at least Figure 6A-B). Neither the fusion polypeptide of

SEQ ID NO: 4 nor any other fusion polypeptide containing NGR was tested for binding to CD 13 on tumor vessel endothelial cells.

Claim 19 requires that the peptide portion (part (a)) of the fusion polypeptide be capable of "selectively binding said fusion polypeptide to tumor vessel endothelial cells." While GRGDSP (SEQ ID NO: 33) has been shown to have this capability for SEQ ID NO: 3, no other peptide disclosed in the specification or embraced by the claims has been shown to have this capability. It is not considered to be so predictable that any 3 to 30 amino acid peptide would have this ability in the presence or absence of a linker having up to 15 amino acids. (See for example claims 19-21.) It is not considered to be so predictable that a cyclic peptide (see claim 24) would have this ability even if the linear peptide did. The results of SEQ ID NO: 3 cannot be extrapolated to other peptides disclosed in the specification as part of fusion polypeptides or other peptides embraced by the claims as the structures of these peptides are highly diverse. For example, the specification does not demonstrate that SEQ ID NOS: 4-8 have this capability. Only the fusion polypeptide of SEQ ID NO: 3 contains the RGD sequence disclosed as being specific for $\alpha_v\beta_3$-integrin.

Claim 19 requires that a tissue factor or a fragment thereof (part (b)) be capable of "activating blood clotting when said fusion polypeptide binds to tumor vessel endothelial cells." Claim 19 is not limited to any particular tissue factor. While the specification focuses on SEQ ID NO: 1 (full length human tissue factor) and SEQ ID NO: 2 (truncated human tissue factor having amino acids 1-218), claim 19 is directed to any tissue factor from any species. The specification provides no specific definition for what constitutes a tissue factor. The specification does not disclose a tissue factor from any species other than human. The

specification does not disclose fragments of human tissue factor other than SEQ ID NO: 2 when present in the fusion polypeptide of SEQ ID NO: 3 that activate blood clotting when bound to tumor vessel endothelial cells. It is not considered to be so predictable that the properties of the fusion polypeptide of SEQ ID NO: 3 can be extrapolated to all tissue factors and fragments thereof that are embraced by the claims. The specification provides no guidance or examples of other tissue factors that would have been expected to be operable. The specification provides no information on those portions of tissue factor required for this activity.

Claim 39 is directed to any neoplastic disorder and claim 40 recites a variety of neoplastic disorders. The specification discloses the ability of the fusion polypeptide of SEQ ID NO: 3 to inhibit human malignant melanoma, human fibrosarcoma, and human lung carcinoma tumors in mouse models. (See at least Figures 7-8 and 34.) Arap et al. (see at least page 377) teaches that RGD specifically targets melanoma, sarcoma, and carcinoma. The specification does not provide any information concerning the remaining tumors embraced by the claims. The specification and prior art of record do not make clear whether all of these neoplastic diseases would have been known to express $\alpha_v\beta_3$-integrin receptors selectively and specifically at high density on tumor endothelial cells. For those neoplastic disorders where this would not have been true, one of ordinary skill in the art would not have been able to extrapolate the results for the fusion polypeptide of SEQ ID NO: 3.

With respect to claims 35-37, the specification discloses using nucleic acids, vectors, and host cells to produce the fusion polypeptide. There is no guidance in the specification for using nucleic acids, vectors, or host cells in any therapeutic capacity such as gene therapy. The specification discloses and exemplifies administration of the fusion polypeptide.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 34-37 and 39-40 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 34-37 are directed to pharmaceutical compositions. However, these claims do not require any components in addition to the claim upon which they depend. For example, claim 19 is directed to a fusion polypeptide. Claim 34 depends on claim 19 but only requires a fusion polypeptide. Claims 34-37 are confusing because they do not appear to further limit the subject matter of the claim upon which they depend. Clarification is requested.

Claim 39 is directed to a method of treating a patient with a neoplastic disease. The only step recited is "using a pharmaceutical composition." This does not clearly indicate what positive, active method steps are intended to be performed.

Conclusion

The art made of record and not relied upon is considered pertinent to applicant's disclosure.

Morrissey et al. (US 2006/0088524) is not prior art but teaches fusing tumor targeting molecules to the N- or C-terminus of tissue factor. Truncated tissue factor is disclosed. See at least pages 29-31, 35-36, and 40-41. This disclosure is not present in parent application 10/465,789.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Marianne P. Allen whose telephone number is 571-272-0712. The examiner can normally be reached on Monday-Friday, 5:30 am - 2:00 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Manjunath N. Rao can be reached on 571-272-0939. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Marianne P. Allen/
Primary Examiner, Art Unit 1647

mpa